Multiple Myeloma: A Paradigm for Drug Development

Peter Anglin MD, FRCPC, MBA

Stronach Regional Cancer Centre
Newmarket, ON

Objectives of Today

• Understand what multiple myeloma is

• Understand the impact on the disease from drug development
  – A “paradigm” for the approach to other malignancies

• Current state of therapy including newer “novel” agents

• Future developments
Case presentation

- 50 year old woman
  - Increasing back pain over 7 months
    - Now unable to work
  - Plain X-rays Oct 2009 showed changes at L1 with compression
  - Lab:
    - Hb 100, WBC 7.3, plats 207
    - Cr 101, t. protein 103, albumen 37, calcium 2.27
      - IgG kappa paraprotein
    - BM: 60% plasma cells with abN forms
A bone marrow examination confirmed the presence of myeloma.

Multiple myeloma is a cancer of the bone marrow affecting blood elements and bone.
Multiple myeloma is defined by the presence of end organ damage

“CRAB”

- Hypercalcemia
- Renal insufficiency
- Anemia
- Bony lesions

Other associated findings:
- Symptomatic hyperviscosity
- Amyloidosis
- Recurring bacterial infections

Multiple Myeloma

- 1% of malignancies
- 4 per 100,000 (1700 Canadians/yr)
- Median age 65 years
Multiple myeloma is a chronic disease treated over several years with sequential therapies.

Why is myeloma an “easy” malignancy to try new drugs…

- Easily accessible tissue (bone marrow)
- Presence of paraprotein reflecting disease burden
- Endpoints are reached in relatively short intervals
Milestones in myeloma therapy

The treatment of myeloma is divided into many different “pieces”

MP – melphalan-prednisone
ASCT = autologous stem cell transplantation
The goal of therapy is to minimize the disease burden and therefore increase duration of remission.

The better the response the better the duration of remission.

Depth of Response in Multiple Myeloma

- At diagnosis
- Partial Response - 50% reduction in M Protein
- Near Complete Remission - Immunofixation positive only
- Complete Remission - Immunofixation negative
- Non-quantitative ASO-PCR
- Quantitative ASO-PCR Flow Cytometry

Depth of response usually correlates with TTP

Courtesy Dr. Donna Reece
There are two reasons why we treat malignant disease that may not be “curable”

Length of Life  
Quality of Life

Patient preferences and specific drug properties (side effects or lack thereof) will figure greatly into this dynamic

Length of Life  
Quality of Life  
Patient Preferences  
Drug Properties
The first 30 years of myeloma therapy was dominated by melphalan (and related drugs) and steroids

Traditional chemotherapy approaches focused on tumour growth inhibition
Traditional chemotherapy approaches focused on tumour growth inhibition

The Mayo Clinic found (in a retrospective review to 1998) that survival had not changed in MM over 13 years

N= 1027
Median age 66
High dose melphalan with autologous stem cell support was the first major “breakthrough” in myeloma therapy in 30 years.
If a little bit of drug works more can work even better.... Dose response.

Autologous stem cell transplant allows higher doses of chemotherapy to be delivered without obliterating the BM stem cells.

The Autologous Transplant Process

1. Collection
   Stem cells are collected from the patient’s bone marrow or blood.

2. Processing
   Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.

3. Cryopreservation
   Blood or bone marrow is frozen to preserve it.

4. Chemotherapy
   High dose chemotherapy and/or radiation therapy is given to the patient.

5. Reinfusion
   Thawed stem cells are reinfused into the patient.
The last 10 years has seen the approval by the FDA of 5 drugs for myeloma:

- **Revlimid®** (lenalidomide)
- **Thalomid®** (thalidomide)
- **Velcade®** (bortezomib)
- **Pamidronate**
- **Zoledronate**

The era of “novel” therapies was ushered in by this publication in 1999:

*The New England Journal of Medicine*

Antitumor Activity of Thalidomide in Refractory Multiple Myeloma

Seema Singhal, M.D., Jayesh Mehta, M.D., Raman Desikan, M.D., Dan Ayers, M.S., Paula Roberson, Ph.D., Paul Eddlemon, B.S., Nikhil Munshi, M.D., Elias Anaissie, M.D., Carla Wilson, M.D., Ph.D., Madhav Dhodapkar, M.D., Jerome Zeldis, M.D., and Bart Barlogie, M.D., Ph.D.

These newer agents had several mechanisms of action hypothesized including modulating the immune system…. “IMIDs”

The IMIDs have become a staple in the therapy of myeloma in the last 5 years

thalidomide (Thalomid®)  
lenalidomide (Revlimid®)
Impact of Revlimid® on overall survival in relapsed/refractory multiple myeloma

Dimopoulos M et al., 2009.

Another example of significant progress with oral therapies.....

- Response Rate: 55%
  - Duration: 12 mo

- Response Rate: 91%
  - Duration: 25 months
Bortezomib (Velcade®) ushered in another class of novel agents: the proteosome inhibitors

Proteosome inhibition is yet another unique pathway to target cancer therapeutics

A Phase 2 Study of Bortezomib in Relapsed, Refractory Myeloma

Paul G. Richardson, M.D., Bart Barlogie, M.D., Ph.D., James Berenson, M.D., Soma Singhal, M.D., Sundar Jagannath, M.D., David Irwin, M.D., S. Vincent Rajkumar, M.D., Gordan Skralovic, M.D., Melissa Alsina, M.D., Raymond Alexanian, M.D., David Siegel, M.D., Robert Z. Orlowski, M.D., David Kuier, M.D., Ph.D., Steven A. Limentani, M.D., Stephanie Lee, M.D., Teru Hideshima, M.D., Ph.D., Daxie-Lee Esseltine, M.D., Michael Kauffman, M.D., Ph.D., Julian Adams, Ph.D., David P. Schenken, M.D., and Kenneth C. Anderson, M.D.
Trends in mortality after relapse:
Improved survival with novel agents

Kumar et al, BLOOD, 1 MARCH 2008 VOLUME 111, NUMBER 5.

2\textsuperscript{nd} and third generation derivatives of novel agents are now getting clinical exposure.

- Less side effects
- Increased response

\begin{itemize}
  \item pomalidomide
  \item carfilzomib
\end{itemize}
Newer induction regimens are achieving essentially 100% response rates!

• Revlimid®, Velcade® and dexamethasone (RVD) is the first regimen to report a 100% response rate in myeloma
  – May represent the new standard of care……

How to apply these many new therapeutics optimally is becoming a challenge and the focus of trials…. 
With so many active drugs finding the optimal sequence of treatment is a challenge.....

A plethora of new pathways and agents are being explored as we move towards “cure” of myeloma.
New drug development is looking at the genetic causes of cancer

Understanding these causes can allow the development of “targeted” therapeutics.
What have we learned today….?

• About multiple myeloma

• How incremental drug innovations have doubled survival in this disease
  – Autologous stem cell transplant
  – Immunomodulatory agents
    • Thalidomide (Thalomid)
    • Lenalidomide (Revlimid)
  – Proteosome Inhibitors
    • Bortezomib (Velcade)

• These innovations are being felt by patients every day but.....

Questions / Discussion